DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration
Central Region

New Jersey District
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

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gs198d

February 1, 2005

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED
Mr. Stuart Hinchen
President
Mayne Pharma (USA) Inc.
650 From Road, 2nd Floor
Paramus, New Jersey 07652

FILE NO.: 05-NWJ-10

Dear Mr. Hinchen:

During the period from September 13 through October 6, 2004, Investigator Tara Gooen from our New Jersey District Office conducted an inspection of your firm located at 650 From Road, Paramus, N.J., to determine your firm's compliance with the Postmarketing Adverse Drug Experience (PADE) reporting requirements of Section 505(k) of the Federal Food, Drug, and Cosmetic Act (the Act) and Title 21, Code of Federal Regulations, section 314.80.

Based on our review of the inspection report, we conclude that your firm violated Section 301(e) of the Act because it failed to comply with 21 CFR 314.80 and Section 505(k)(1) of the Act. Section 505(k)(1) and 21 CFR 314.80 require an applicant to establish and maintain records, and to report certain adverse drug experience information for drugs for which an approved application is in effect.

Deviations from 21 CFR 314.80 include the following:

1. Failure to submit Adverse Drug Experience (ADE) reports to the FDA as required by 21 CFR 314.80(c). Specifically, the following are examples of ADEs or information regarding ADEs that were not submitted to FDA.

(a) Two serious and unexpected adverse drug experiences were not submitted to FDA or forwarded to the contracted affiliate responsible for reporting, as required under 21 CFR 314.80(c)(1)(i):

	Product	Medical Event	Date Received
[redacted]	Famotidine Injection	Renal impairment	7/6/04
[redacted]	Famotidine Injection	Multi-organ failure	7/6/04

(b) The follow-up information from a 15-day alert report was not submitted to FDA, as required under 21 CFR 314.80(c)(1)(ii)

	Product	Medical Event	Date Received
[redacted]	Pamidronate Disodium Inj. Solution	Hypercalcemia aggravated, LDH increased, Parathyroid Hormone decreased	5/22/03

(c) Incorrect entry of the "Date Received by Manufacturer" on MedWatch forms for 15-day alert reports caused some reports to be submitted after 15 days had elapsed, in violation of 21 CFR 314.80(c)(1)(i). Your firm should use the date that their business affiliate received the initial report as the time the 15-day reporting clock begins.

	Suspect Mayne Drug	Reported Medical Event (MedDRA terms)	Actual Date of Initial Case Receipt	Date of Initial Case Receipt as Reported	Date Reported	Approx. No. Days Late
[redacted]	Methotrexate Sodium Injection	Lung Infection NOS, Polyarthritis, Tooth Abscess, Pyrexia	30-Dec-03	9-Jan-04	27-Jan-04	13
[redacted]	Methotrexate Sodium Injection	Escherichia bacteraemia, Escherichia urinary tract infection	04-Mar-04	16-Mar-04	31-Mar-04	12
[redacted]	Methotrexate Sodium Injection	Lupus-like syndrome	08-Mar-04	16-Mar-04	31-Mar-04	8

(d) Missing concomitant medications on MedWatch forms for serious, labeled adverse drug experiences, as documented on the initial telephone records by Medical Affairs of the Paramus, NJ facility, as required under 21 CFR 314.80(c)(2)(ii):

	Suspect Mayne Drug	Reported Medical Event (MedDRA terms)	Missing Information	Date of Initial Case Receipt
[redacted]	Pamidronate Disodium Injection, Solution	Extravasation NOS	Peroxidine	28-Apr-04
[redacted]	Pamidronate Disodium Injection, Solution	Severe Bone Pain, Pyrexia, Diarrhoea NOS	Aluvite (? illegible)	30-Mar-04

2. Failure to submit serious and unexpected ADE reports within 15 calendar days of the initial receipt of this information by your firm, as required under 21 CFR 314.80(c)(1)(i). Approximately [redacted] assessed as 15-day alert reports by your firm between 9/1/02 and 9/17/04 were submitted late to FDA, including the following:

[redacted]	Product	Date Received	No. Days Late
[redacted]	Morphine	11/21/96	2539
[redacted]	Cytarabine Inj.	4/17/03	124
[redacted]	Cytarabine Inj.	3/17/03	86
[redacted]	Vincristine Sulfate Inj.	9/2/03	54
[redacted]	Methotrexate Sodium Inj.	3/29/04	24

3. Failure to conduct a follow-up investigation into all serious and unexpected ADEs. For example, your firm did not perform a follow-up investigation for the 15-day alert reports with [redacted], as required by 21 CFR 314.80 (c)(1)(ii).

4. Failure to submit periodic reports to FDA in violation of 21 CFR 314.80(c)(2). No periodic reports were submitted concerning the product Paclitaxel Injection, USP, 6mg/mL (ANDA 76-131 and ANDA 76-233), for the dates 10/1/03 to 11/8/03.

In addition, at least one periodic adverse experience (non-serious) was not reported to FDA:

[redacted]	Product	Medical Event	Date Received
[redacted]	Paclitaxel Inj. Injection	Site reaction, Hypoaestmesia	10/30/03

5. Failure to submit quarterly periodic ADE reports within 30 days of the close of the quarter for the following, as required by 21 CFR 314.80(c)(2)(i):

Product	Reporting Interval		Submitted	Late
	Start	End		
Pamidronate Disodium Inj. USP, 3 mg/mL, 6 mg/mL, 9 mg/mL ANDA #75-841	9/28/02	12/27/02	7/11/03	166 days
Paclitaxel Inj. USP, 6 mg/mL ANDA #76-131	7/1/03	9/30/03	11/17/03	18 days
Paclitaxel Inj. USP, 6 mg/mL ANDA #76-233	7/1/03	9/30/03	11/18/03	19 days
Pamidronate Disodium Inj. USP, 3 mg/mL, 6 mg/mL, 9 mg/mL ANDA #75-841	3/28/04	6/27/04	8/4/04	8 days

6. Failure to develop adequate written procedures for surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA as required by 21 CFR 314.80(b). Specifically, there are no written procedures for the following:

(a)Reviewing and maintaining the Submission Log to ensure that all appropriate information is documented. No procedure exists regarding what information should be recorded and tracked. Currently, the submission date is not always documented and no review of the Submission Log is conducted.

(b) Verification of the monthly medical information metrics, where inaccurate statistics of 100% timely submission of 15-day alert and periodic reports were misreported in July, August, September, November, December 2003. Metrics have not been conducted since April 2004, as required per written procedure. No procedure exists for verifying that the monthly medical information metrics have been performed.

(c) Methods of conducting follow-up investigations of serious, unlabeled events.

(d) Training of administrative personnel for proper completion of Complaint and Adverse Event forms. Specifically, personnel have not been trained to capture and report all relevant information necessary to complete the Complaint and Adverse Event form.

(e) Reconciliations with Mayne's foreign and domestic offices and affiliates to ensure the receipt of all reportable experiences.

(f) Maintaining and updating a list of Mayne's USA applications and reporting responsibilities to ensure that the contracted affiliate reports or forwards cases, as appropriate.

We received your response letter dated November 3, 2004 and have completed our review of your corrective actions. We consider your proposed corrective actions to be adequate; however, we do have the following questions regarding your responses.

For your response to FDA-483, Observation 1 (c), regarding the reporting of both mmol and pmol as parathyroid serum levels, you include in your corrective action plan (attachment 7) a corrected CIOMS form for [redacted] dated 5/22/2003. The most recent CIOMS form for [redacted] in our Adverse Event Reporting System (AERS) database is dated 5/14/2003. Please let us know if you have submitted your revised CIOMS report, dated 5/22/2003, to FDA.

In your response to the FDA-483, Observation 4 regarding your investigations of serious adverse drug experiences, we understand your proposed revised procedures but it is not clear whether you have, or intend to, submit followup reports to the four cases referenced by Investigator Gooen in this observation.

In your response to Observation 5 (a), you state that you did not have an identifiable patient for reporting purposes. Our review of your handwritten notes on the Customer Inquiry Form in question [redacted] indicates that the patient experienced "pressure under his ribcage". Knowledge that the patient was a male is sufficient to qualify as an "identifiable patient" and therefore would have given you the four elements necessary for submission of an ADE report to the FDA. *See* Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines, March 2001, at p. 9. Another deficiency noted on this form was that the reporter's name was incorrectly entered on the line reserved for patient identification. The ADE report referenced in Observation 5 (b) is another example of an ADE report that should have been adequately investigated and classified as an ADE and not a product complaint.

FDA expects drug manufacturers to establish reasonable mechanisms to assure that all adverse drug experiences are recorded, evaluated and submitted to the FDA within established timeframes as required under 21 CFR 314.80. On page 8 of your response you discuss the fact that your firm was unable to meet regulatory requirements for the reporting of serious and unexpected adverse events because you lacked the resources to process the increasing number of ADEs associated with your acquisition of several new NDAs/ANDAs. Your most immediate corrective action is to ensure that you have adequate numbers of qualified individuals to process all drug safety issues.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. These actions include but are not limited to seizure and/or injunction. Federal agencies are advised of the issuance of all warning letters about drugs and devices so that they may take this information into account when considering the award of contracts.

Neither the above list of deviations nor the Form FDA 483 Inspectional Observations, which was presented to and discussed with you, Stuart Hinchen, at the conclusion of the inspection, are intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence with each requirement of the act and its regulations. We will confirm the adequacy of all your proposed corrections during our follow-up inspection.

You should notify this office in writing within 15 working days of receipt of this letter of your answers to the specific questions identified above, as well as any additional steps taken to correct the noted violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to the Food and Drug Administration, New Jersey District Office, 10 Waterview Blvd, 3rd Floor, Parsippany, New Jersey 07054, Attention: Andrew Ciaccia, Compliance Officer.

Very truly yours,

Ray Abrahams for

Douglas I. Ellsworth
District Director
New Jersey District Office